Principles of Post-Trial Responsibilities: Continued Access to an Investigational Medicine

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) *Post-Trial Responsibilities: Continued Access to an Investigational Medicine Framework* outlines a case-based, principled, stakeholder approach to evaluate and guide ethical responsibilities to provide continued access to an investigational medicine at the conclusion of a patient's participation in a clinical trial. The foundation of this guidance document is summarized in 12 principles:

1. Post-trial responsibilities to a research participant (patient) at the end of participation in a clinical trial are **shared among all stakeholders**: sponsor, investigator, site, health care provider, health care system and the participant.
2. Provision of continued access is a **bounded and not a limitless responsibility** of any one stakeholder.
3. **Responsibilities are generally equivalent** whether the sponsor is a for-profit, not-for-profit, or governmental agency, and whether the trial is conducted in a well- or low-resourced setting.
4. **Provision of continued access must be fair** and not inadvertently advantage some and harm others.
5. The plan to offer or not to offer continued access to an investigational medicine should be **determined before a trial begins and appropriately communicated** to investigators, ethics committees, and participants.
6. If there is **evidence of benefit exceeding risk**, and importantly in settings of unmet medical need, continued access to a beneficial treatment should be considered for a participant.
7. Decisions regarding the provision of continued access to an investigational medicine or comparator to a participant are made on a **case-by-case basis**, influenced by the patient's clinical condition, the benefit/risk assessment and response to the intervention, and what is known about the investigational medicine at the time of the decision.
8. Generally, **informed consent for continued access** should be solicited prior to provision of the medicine.
9. If continued access to an investigational medicine is offered, **medical care and infrastructure** specifically necessary for the appropriate provision of the investigational medicine must also be provided.
10. Continued access to an investigational medicine should always be provided under mechanisms that **satisfy local regulatory requirements** for investigational medicines.
11. The sponsor is responsible for **continuously assessing whether there is an ongoing unmet medical need** for the investigational medicine during the clinical trial and drug development program.
12. For the health and safety of an individual participant, **responsible transition** from the investigational medicine to other appropriate care may be, and is often, necessary.

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For more information about the MRCT Center's work on the post-trial responsibilities, visit: http://mrctcenter.org/projects/post-trial-responsibilities/

Continued Access Criteria

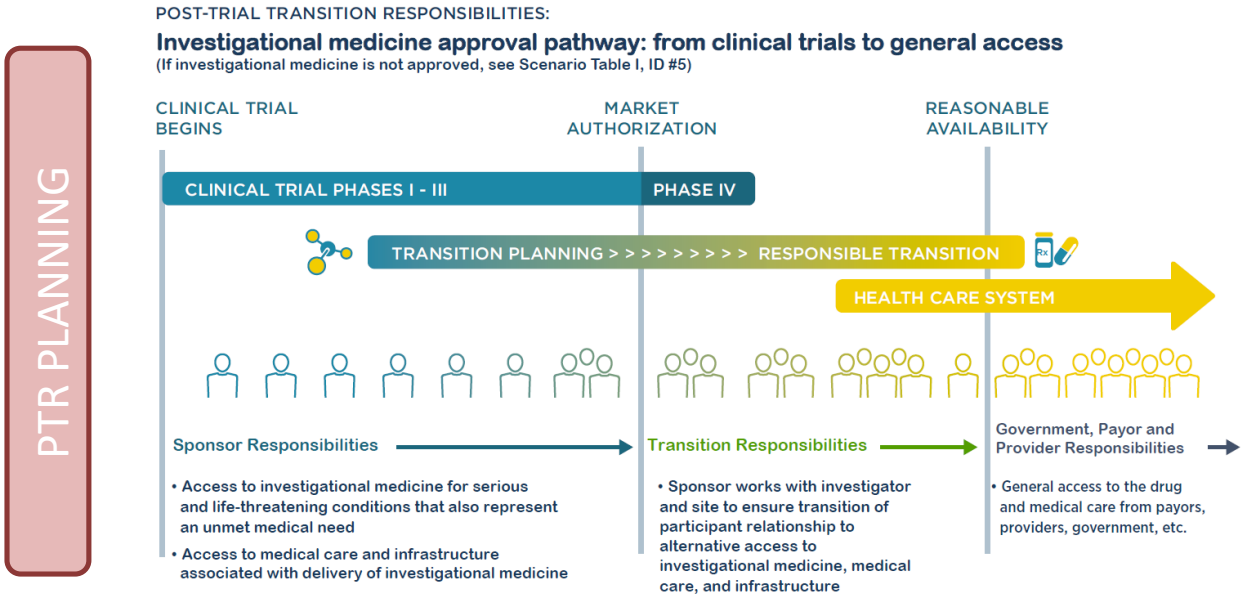
The sponsor and the investigator should weigh a number of interdependent criteria to inform decisions about the provision of continued access at both a Study Program and Individual Participant level. These criteria include:

Study Program Level (Sponsor)

1. *Impact of discontinuation*: The disease/condition under study is serious or life threatening and the research participant could be adversely impacted if the medicine were to be discontinued.
2. *Medical need*: The investigational medicine addresses an unmet medical need in that there are no suitable therapeutic alternatives available to participants.
3. *Access:* There is no alternative access to the investigational medicine.
4. *Research viability*: The provision of continued access to the investigational medicine will not affect the viability of the research or the ability to complete the trial or other trials.
5. *Benefit/risk assessment (population):* After data lock and analysis of the results, the overall study population benefit/risk assessment is known.

Individual Participant Level (Investigator)

1. *Trial participation*: The eligible participant has completed the clinical trial protocol.
2. *Benefit/risk assessment (individual*): There is demonstrable evidence of benefit exceeding risk for an individual participant as determined by the investigator.



Inspired by Ignacio Mastroleo and refined by the workgroup

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Stages of Continued Access

There are five stages during a clinical trial when continued access needs to be considered either at a Study Program (i.e., relative to the medicine and disease/condition under study) and/or Individual (i.e., relative to the individual participant) Level.

Stage 1: Study Planning

At the Study Program Level, the sponsor is responsible for planning before the trial begins. The sponsor should evaluate whether it is possible, in principle, that research participants will meet the criteria for continued access given the drug and disease/condition under study. If so, the sponsor should develop a plan in discussion with relevant stakeholders, including establishing criteria for when a patient should be transitioned to another mechanism of access or to other alternatives. In multinational clinical trials, national legislation and local health care capabilities should be considered.

Stage 2: Monitoring of available alternatives

At the Study Program Level, the sponsor is responsible for ongoing monitoring throughout the course of the clinical study and drug development program to assess whether there is still an unmet medical need that requires continued access to the investigational medicine. Other alternatives may become available that modify or eliminate the ethical justification to provide continued access.

Stage 3: Decision Point 1

At the Individual Participant level, the investigator is responsible for the first operative decision. At the participant's last patient visit, the investigator evaluates and communicates (to the patient and sponsor) whether the individual's benefit/risk assessment warrants continued access to the intervention(s) received during the trial (investigational medicine or comparator, and associated medical care) in accordance with Study Program planning.

In some trial designs, where it is not possible to know if the participant has had benefit at the last visit (e.g., in asymptomatic condition where the endpoint is prevention, or in trials in which the endpoint is progression-free survival), there would be no rationale to continue therapy after completion of the trial unless the results are known (see Decision Point 2).

Stage 4: Decision Point 2

At the Study Program Level, the sponsor is responsible for a second operative decision. After database lock and data analysis, the sponsor evaluates whether the overall study population benefit/risk assessment warrants ongoing continued access to the intervention or, in some cases, offering all participants access to the intervention. In others, safety concerns or lack of efficacy may warrant reconsideration of the initial decision to provide continued access.

Stage 5: Transition

At the Individual Participant level, the investigator is responsible for a third operative decision as to whether and when participants should be transitioned off the intervention. Events such as the commercial availability of the investigational medicine, other satisfactory alternatives for treatment (see Stage 2), or the participant no longer requires treatment may trigger a transition decision. These possibilities, and the timing thereof, should be outlined in the informed consent to the trial, in collaboration with the sponsor.

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